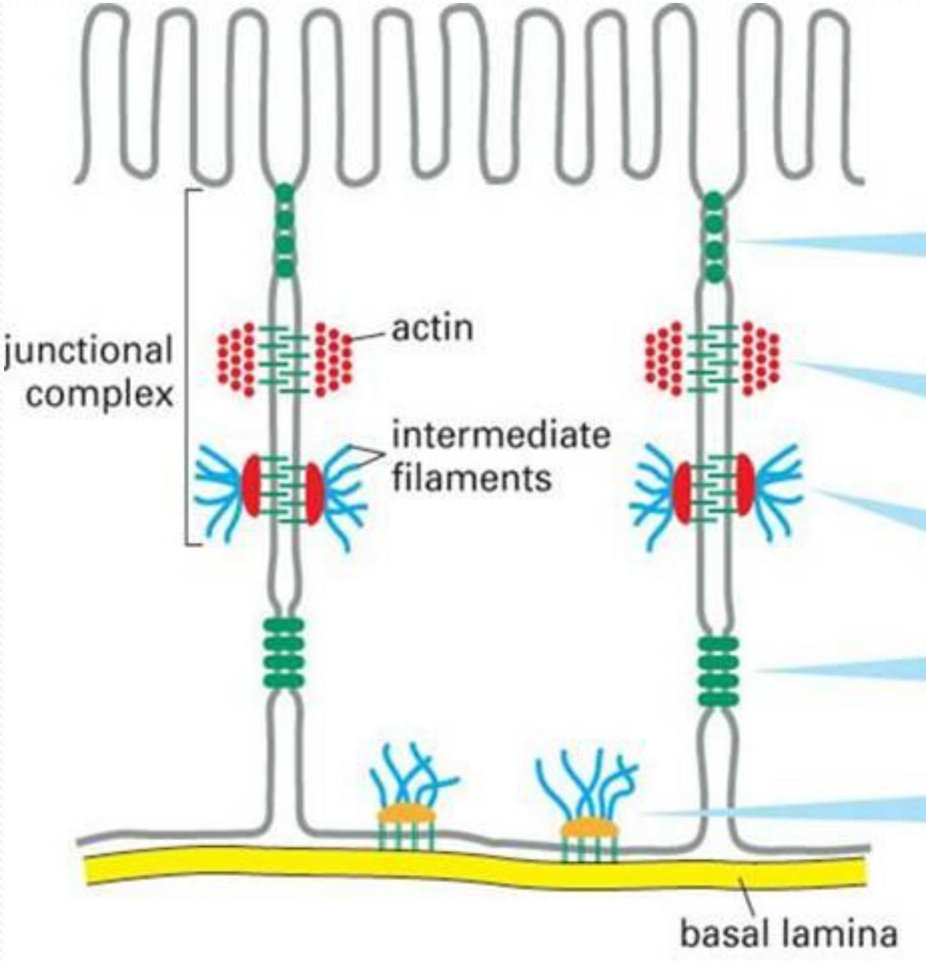
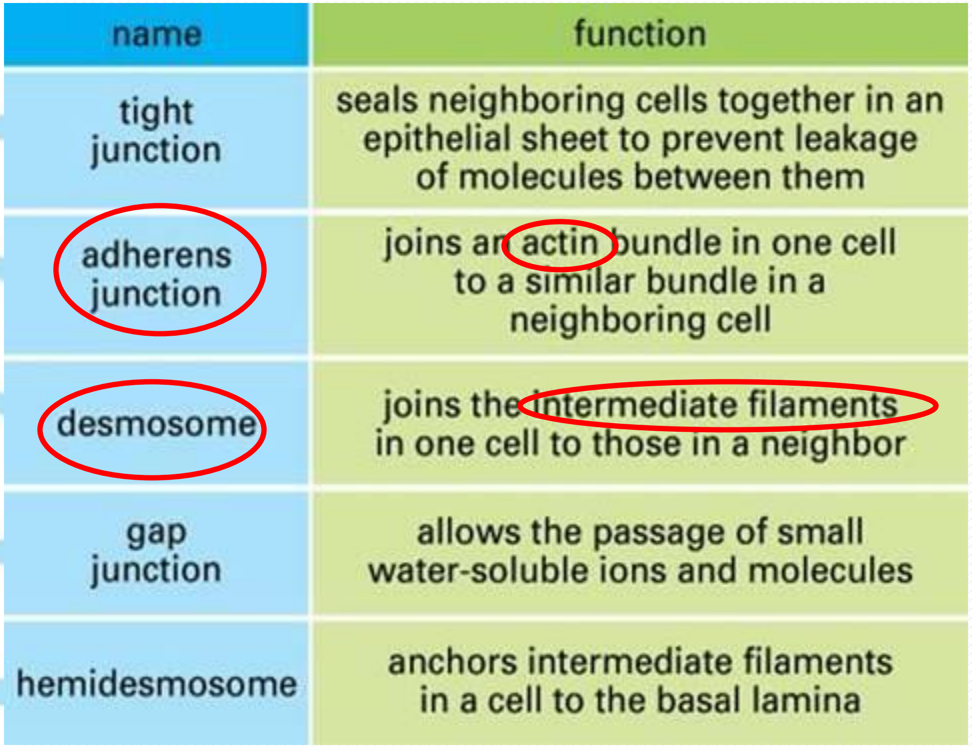
Cadherins

Introduction
Types of cell junctions



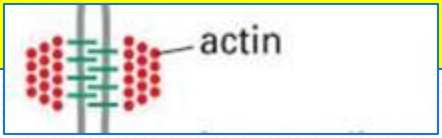


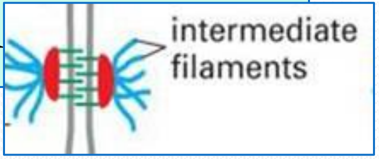
name	function
tight junction	seals neighboring cells together in an epithelial sheet to prevent leakage of molecules between them
adherens junction	joins an actin bundle in one cell to a similar bundle in a neighboring cell
desmosome	joins the intermediate filaments in one cell to those in a neighbor
gap junction	allows the passage of small water-soluble ions and molecules
hemidesmosome	anchors intermediate filaments in a cell to the basal lamina

Adherens junctions vs. Desmosomes

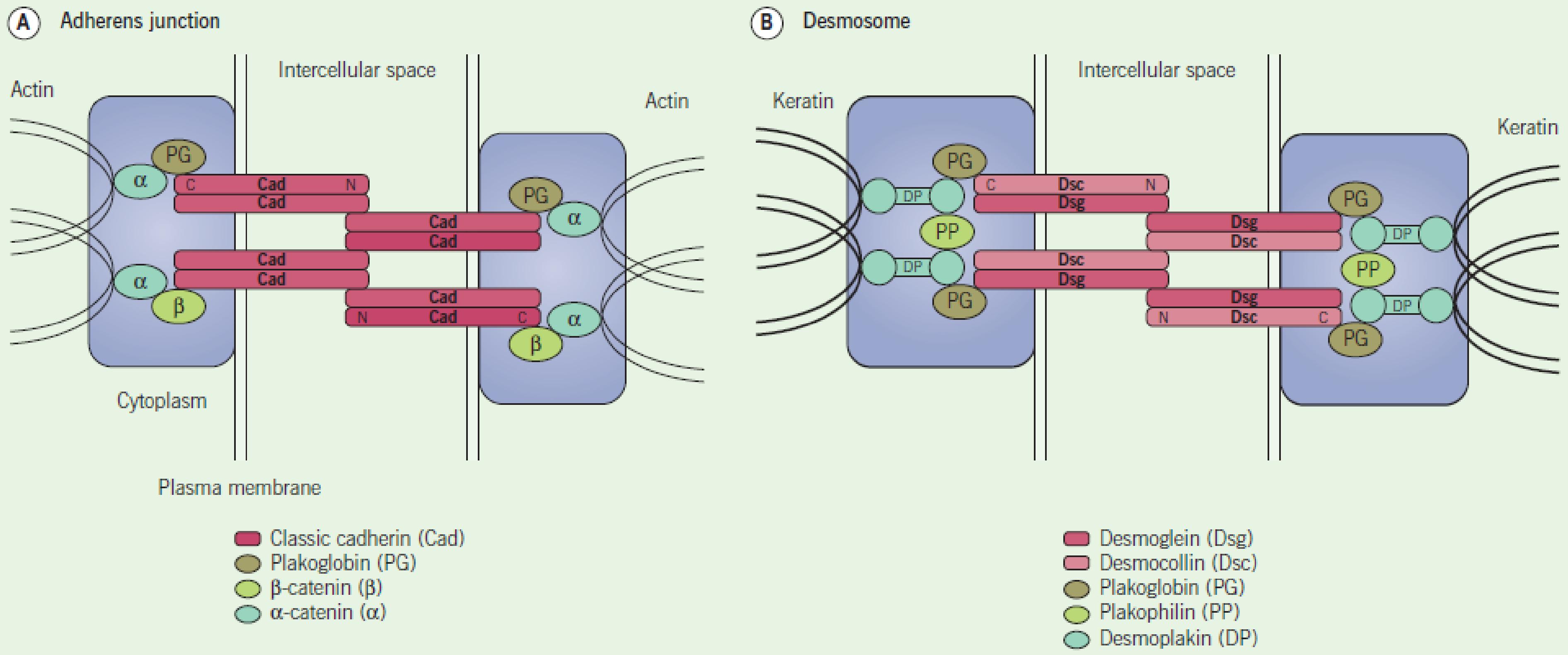
They are 2 major types of adhering junctions in epithelial cells: The adherens junctions and the desmosomes

Adherens junctions	Desmosomes
anchor bundles of **actin** microfilaments	anchor **intermediate filaments** like **keratins**
contain **classic cadherins** as its **transmembrane** components	contain **desmosomal cadherins** as its **trans-membrane** components
Contain **α-catenin, β-catenin and plakoglobin** as its **cytoplasmic** components	Contain **plakoglobin, plakophilin & desmo-plakin** as its **cytoplasmic** components
mediate **quick** but **weak** cellular adhesion	mediate **slow** but **strong** cellular adhesion





Adherens junctions vs. Desmosomes



What are cadherins? What are their types?

Cadherins are a family of **calcium-dependent** cell–cell **adhesion molecules** that play an important role in the formation and maintenance of complex tissue integrity

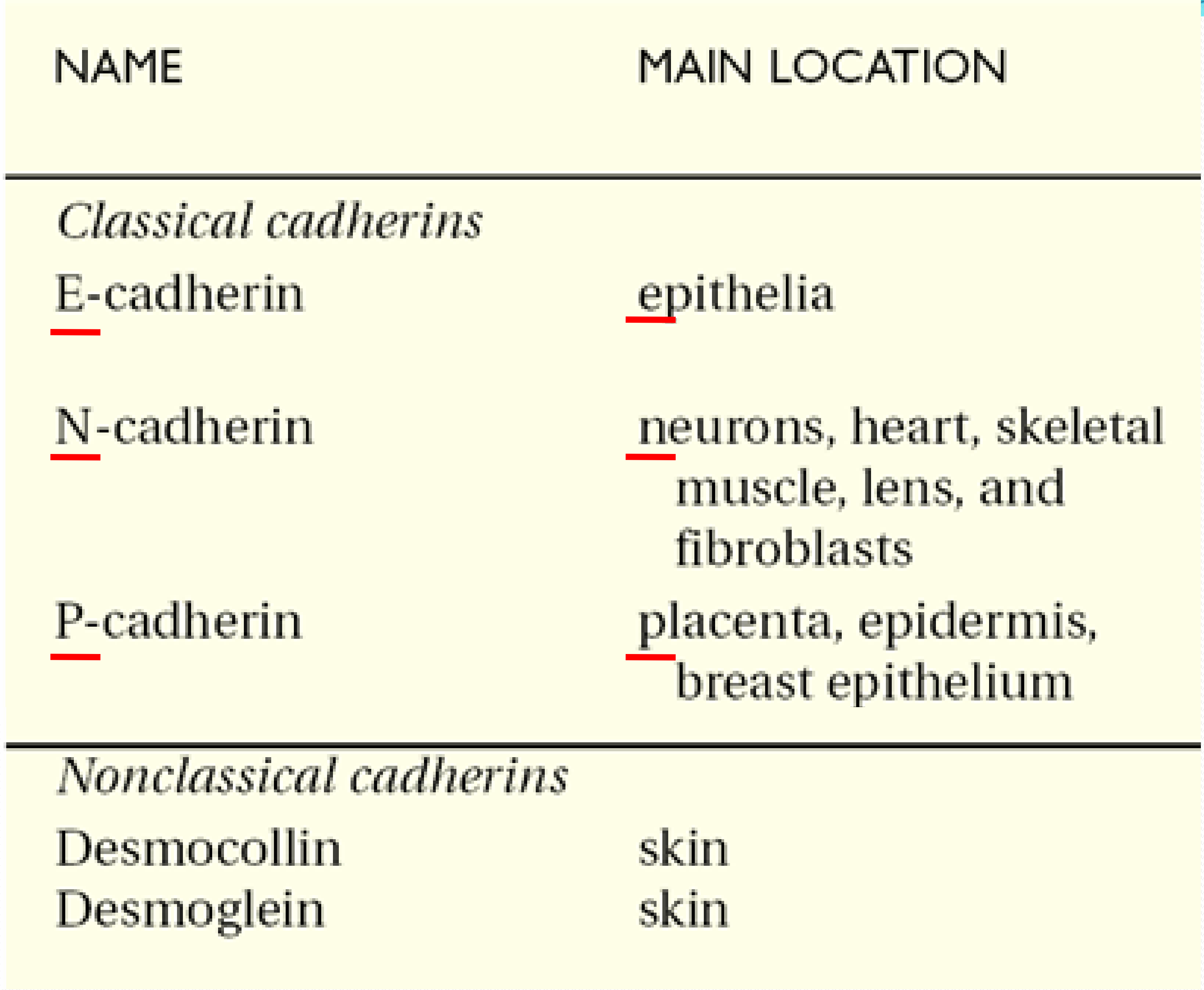
Cadherins have **2 major subgroups:**

1. **classic cadherins** (e.g. E-, P-, N-cadherins)

   In **adherens junctions**

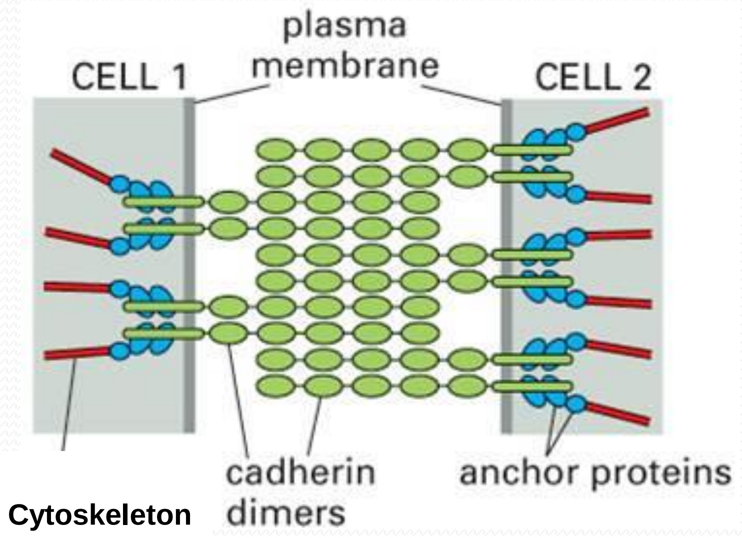
2. **desmosomal cadherins** (e.g. desmogleins and desmocollins)

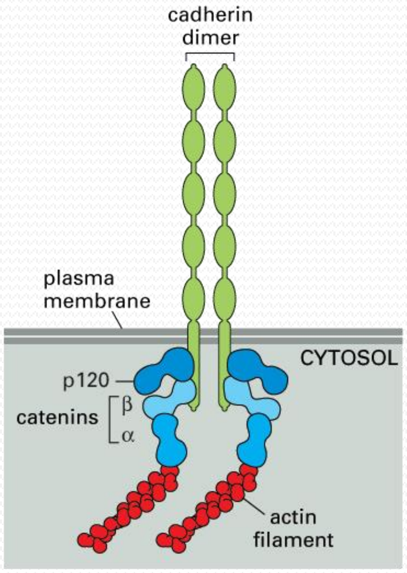
   In **desmosomes**



NAME	MAIN LOCATION
Classical cadherins	
E-cadherin	epithelia
N-cadherin	neurons, heart, skeletal muscle, lens, and fibroblasts
P-cadherin	placenta, epidermis, breast epithelium
Nonclassical cadherins	
Desmocollin	skin
Desmoglein	skin

- Cadherins require their **cytoplasmic domains** to associate with the **plaque (anchor) proteins** (e.g. α-catenin, β-catenin and plakoglobin), which mediate binding to the **cytoskeleton network**.
- Cadherin molecules form **dimers** as their functional unit, with the distal **extracellular domain** (EC) of the cadherin from one cell binding to the same region of a second cadherin from an opposing cell



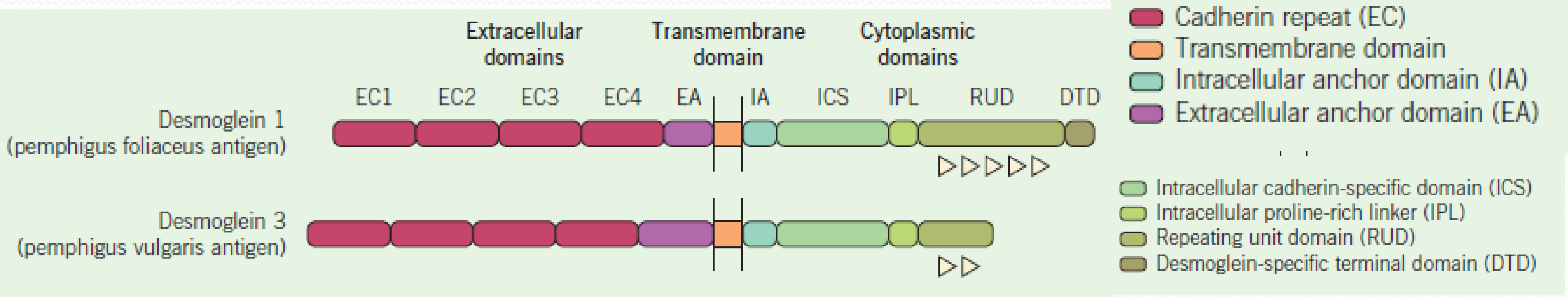


- As a consequence of these interactions, cadherins produce strong cellular adhesion and morphologic changes in the cells

Desmosomal cadherins
Desmogleins

Structure:

- Have 4 extracellular domains (EC1, 2, 3, 4) = cadherin repeats
- Extracellular anchor (EA) domain
- Transmembrane domain
- Intracellular anchor (IA) domain
- Intracellular cadherin-specific (ICS) domain: responsible for interactions with β-catenin or plakoglobin
- Repeating unit domain (RUD): unique repeats of 29 ± 1 amino acid residues


Extracellular domains
Transmembrane domain
Cytoplasmic domains
EC1
EC2
EC3
EC4
EA
IA
ICS
IPL
RUD
DTD
Desmoglein 1 (pemphigus foliaceus antigen)
Desmoglein 3 (pemphigus vulgaris antigen)
▷▷▷▷▷
▷▷
Cadherin repeat (EC)
Transmembrane domain
Intracellular anchor domain (IA)
Extracellular anchor domain (EA)
Intracellular cadherin-specific domain (ICS)
Intracellular proline-rich linker (IPL)
Repeating unit domain (RUD)
Desmoglein-specific terminal domain (DTD)

Desmosomal cadherins
Desmogleins

Isoforms:

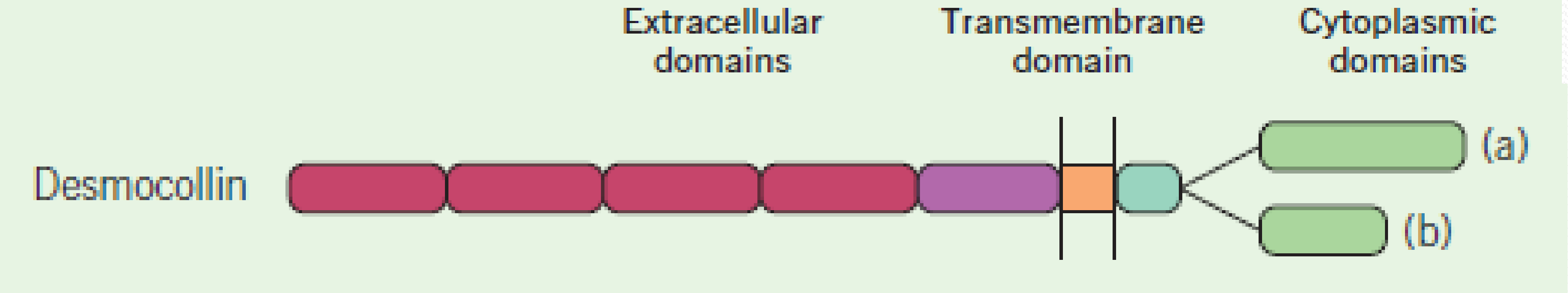
Cadherins have 4 isoforms (Dsg1–4)

- **Dsg1 and Dsg3:** basically restricted to stratified squamous epithelia, where blisters are formed in pemphigus
- **Dsg2:** expressed in all desmosome-possessing tissues, including simple epithelia and myocardium
- **Dsg4:** plays an important adhesive role in hair follicles (mutations in the *DSG4 gene can lead to abnormal hair development e.g.* localized autosomal recessive hypotrichosis)

Desmosomal cadherins

Desmocollins

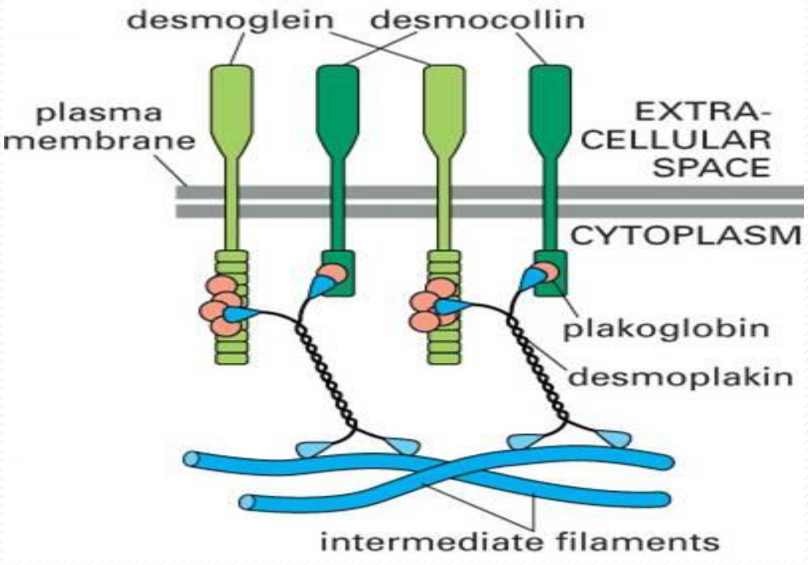
- Another group of trans-membrane glycoproteins within desmosomes
- Have 3 isoforms (Dsc1–3)
- Each isoform has 2 products derived from alternatively spliced mRNA of a single gene



Desmosomal cadherins

Desmocollins

- Desmosomes always have desmoglein and desmocollin as a pair, but the exact molecular fashion of their interaction as well as the reason why desmocollin does not compensate for the loss of desmoglein in pemphigus remain to be elucidated



Role of nonclassical cadherins in diseases

(1) Desmogleins → pemphigus

- All patients with pemphigus have IgG autoantibodies against Dsg1 and/or Dsg3, depending on the subtype of pemphigus
  - ☐ Antidesmoglein IgG autoantibodies that have been purified from pemphigus sera can cause blisters when injected into neonatal mice
  - ➢ When anti-desmoglein IgG autoantibodies are removed from the sera of patients with pemphigus vulgaris, pemphigus foliaceus or paraneoplastic pemphigus (by immunoadsorption with recombinant desmoglein proteins), the sera are no longer pathogenic in inducing blister formation

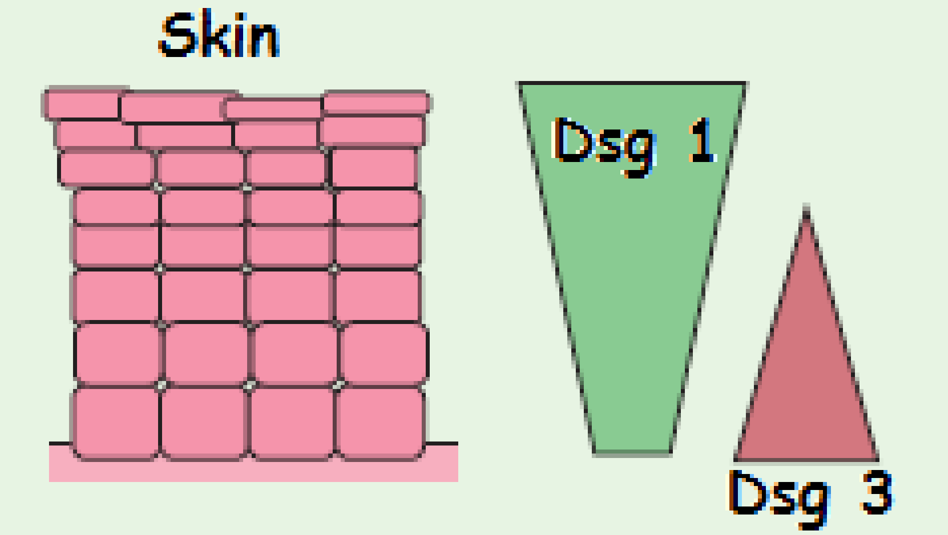
Desmoglein Compensation Theory as Explanation for Localization of Blisters

- Dsg1 and Dsg3 compensate for each other when they are coexpressed in the same cell

- The intraepithelial expression pattern of Dsg1 and Dsg3 differs between the skin and mucous membranes

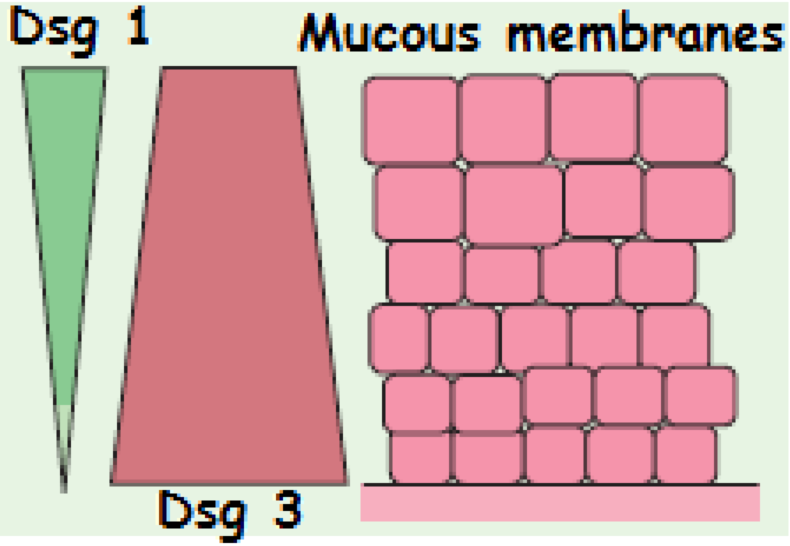
Desmoglein Compensation Theory as Explanation for Localization of Blisters

- In the skin:
  - Dsg1 is expressed throughout the epidermis, but more intensely in the superficial layers
  - Dsg3 is expressed in the lower portion of the epidermis (basal and parabasal layers)



Desmoglein Compensation Theory as Explanation for Localization of Blisters

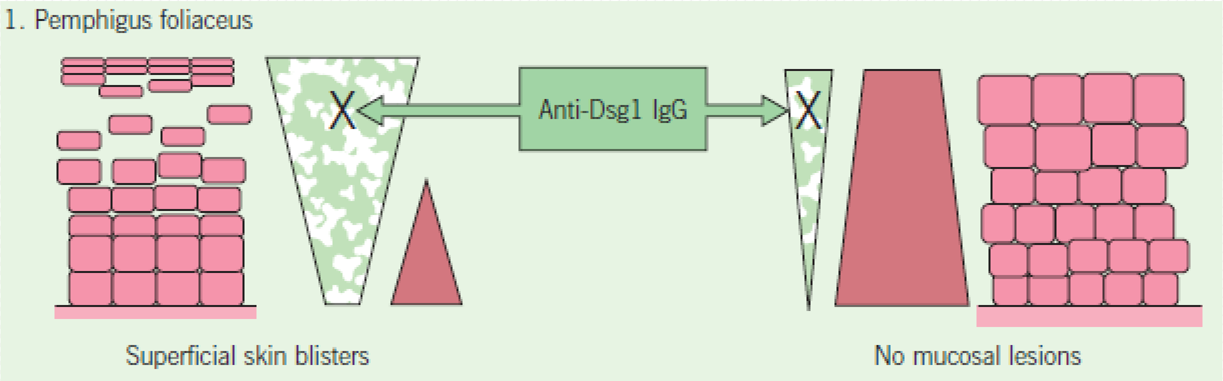
- In the mucous membranes
  - Dsg1 and Dsg3 are expressed throughout the squamous layer of mucosa, but Dsg1 is expressed at a much lower level than Dsg3



Desmoglein Compensation Theory as Explanation for Localization of Blisters

Patients with pemphigus foliaceus have only anti-Dsg1 IgG autoantibodies → superficial blisters in the skin without mucosal involvement

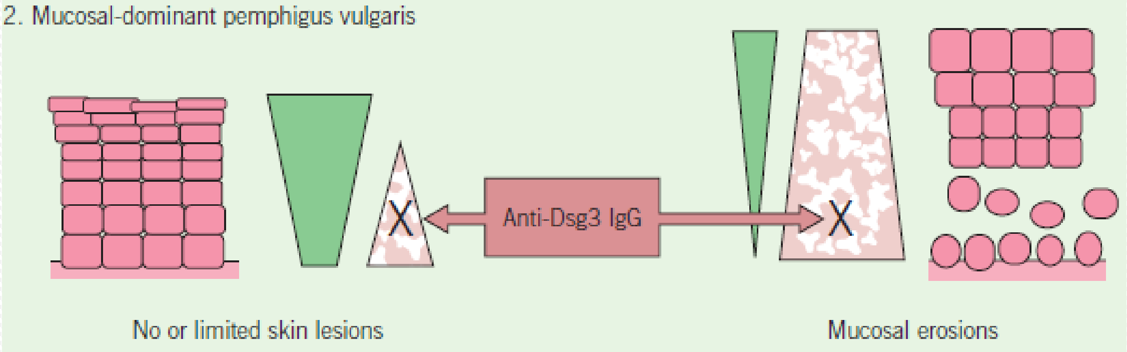
- Blisters appear only in the superficial epidermis of the skin (the only area in which Dsg1 is present without coexpression of Dsg3)
- In the deep epidermis, the presence of Dsg3 compensates for the loss of function of Dsg1 (unaffected)
- No blisters are formed in mucosa (coexpression of Dsg3)



Desmoglein Compensation Theory as Explanation for Localization of Blisters

Patients with the mucosal-dominant type of pemphigus vulgaris have only anti-Dsg3 IgG autoantibodies → oral erosions without apparent skin involvement

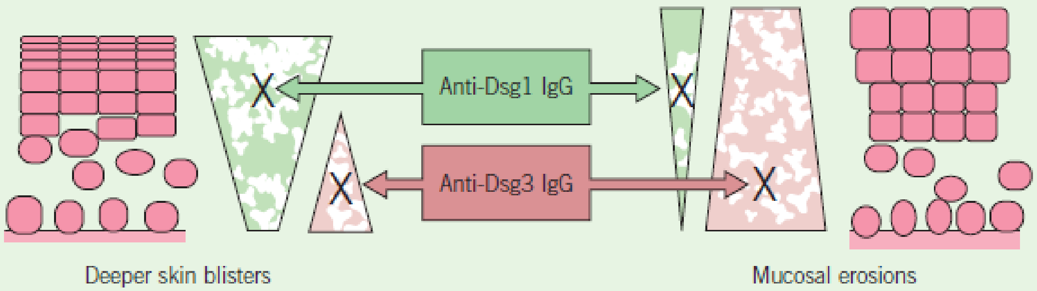
- These autoAbs are inefficient in producing cutaneous blisters (coexpressed Dsg1 compensates for the impaired function of Dsg3) i.e. no, or only limited, skin lesions.
- In the MMs, Dsg1 cannot compensate for the impaired Dsg3 function because of its low expression.


2. Mucosal-dominant pemphigus vulgaris
Anti-Dsg3 IgG
X
X
No or limited skin lesions
Mucosal erosions

Desmoglein Compensation Theory as Explanation for Localization of Blisters

Patients with the mucocutaneous type of pemphigus vulgaris have both anti-Dsg3 and anti-Dsg1 IgG autoAbs → extensive blisters and erosions of the skin and MMs

- **Why splits appear just above the basal layer instead of the whole epithelium falling apart?**
  - cell–cell adhesion in the basal and parabasal layers might be weaker than in other parts of the epithelium (due to fewer desmosomes)
  - autoAbs, which penetrate from the dermis, might have better access to the lower part of the epithelia.



3. Mucocutaneous pemphigus vulgaris

Another clinical application of **Desmoglein Compensation Theory**

- In pregnant women with pemphigus, autoantibodies cross the placenta and bind to the fetal epidermis
- Neonates develop blisters if the mother has pemphigus vulgaris, but very rarely if she has pemphigus foliaceus.
- This observation is explained by the desmoglein compensation theory
  - The distribution of Dsg3 within neonatal epidermis is unlike that in adult epidermis; it is found on the surface of keratinocytes throughout the epidermis, which is similar to its distribution in mucous membranes (neonatal skin is bathed in amniotic fluid)

  - Therefore, pemphigus foliaceus sera containing only anti-Dsg1 IgG cannot induce blisters in neonatal skin.

Thank you